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XY Gonadal Dysgenesis Associated With a Multiple Pterygium Syndrome Phenotype

Brad Angle,[1]* Joseph H. Hersh,[1] Frank Yen,[1] and Gerald D. Verdi[2]

[1] *Department of Pediatrics, Child Evaluation Center, University of Louisville, Louisville, Kentucky*
[2] *Department of Surgery, Child Evaluation Center, University of Louisville, Louisville, Kentucky*

Most phenotypic females with an XY male karyotype do not have significant extragenital anomalies; however, some patients with additional abnormalities have been described. We report on an individual with XY gonadal dysgenesis, mental retardation, microcephaly, growth retardation, and multiple pterygia. Although not previously reported, the possible relationship between these findings is discussed in the context of evident heterogeneity of XY gonadal dysgenesis. Am. J. Med Genet. 68:7–11, 1997

KEY WORDS: XY gonadal dysgenesis; multiple pterygium; phenotype

INTRODUCTION

Sex differentiation is a complex physiologic process that most likely involves the products of many genes, not only on the Y chromosome, but also several that are X-linked and autosomal. Much of the information regarding the mechanisms involved in normal sex determination has been obtained from the studies of individuals with a defect of this process: phenotypic males with a female karyotype (46,XX) and phenotypic females with a male karyotype (46,XY).

Following the discovery that the Y chromosome was necessary for normal male sexual differentiation, a specific gene (SRY) on the short arm of the Y chromosome was identified that is required for initiation of the testis-determining pathway. Autosomal and X-linked loci also have been implicated in the pathway of normal sex determination. There may be a number of still unknown genes that play a role in sex differentiation.

XY gonadal dysgenesis is one form of sex reversal (Swyer syndrome) in which affected individuals are phenotypic females with a uterus and fallopian tubes, but only remnants of ovaries, i.e., streak gonads. Most of these individuals are otherwise normal and do not have somatic anomalies. However, a number of XY females have been reported to have nongenital anomalies; of these, none has been described with features of multiple pterygia.

The multiple pterygium phenotype is characterized by flexion contractures at birth associated with variable webbing of the neck, elbows, knees, and intracrural areas. Although digital and vertebral abnormalities, short stature, and facial anomalies are common findings, visceral anomalies are not. Intelligence in affected individuals is normal. Some cases appear to demonstrate an autosomal recessive inheritance pattern; however, autosomal dominant cases have been identified.

We report on a patient with XY gonadal dysgenesis and multiple pterygia. A brief summary of these conditions and the implications of their coexistence in the same patient are discussed.

CLINICAL REPORT

At term, a female infant was born to a 28-year-old G2P1 mother after an uncomplicated pregnancy and vaginal delivery. There was no consanguinity. A male half-sib (maternal) had a unilateral clubfoot. The infant had a weight of 3.7 kg (75th centile), length 51 cm (50th centile), and head circumference (OFC) 39 cm (>90th centile). There was asymmetry of the calvaria and frontal bossing. A double parietal hair whorl was noted. The ears were small and apparently low-set with overfolded helices. There was micrognathia. The neck was short with anterior webbing. Skin dimpling was present over the elbows. There was subcutaneous syndactyly between the second and third digits and third and fourth digits of both hands, clinodactyly of the great toes, second and fifth fingers, and fifth toes. A right single palmar crease and a left bridged palmar crease were noted. There was webbing of both elbows with limited extension. The sternum was short and the shoulders were anteriorly rotated. Contractures of the shoulders, knees, and ankles were present, and there was some limitation of thumb extension. The external genitalia appeared to be normal. Neurological exam showed generalized hypotonia.

*Correspondence to: Brad Angle, M.D., Child Evaluation Center, University of Louisville, 571 S. Floyd St, Suite 100, Louisville, KY 40202.

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Chromosome analysis performed on cultured leukocytes using both G- and Q-banding techniques showed a 46,XY karyotype in 20 metaphases analyzed. This 46,XY karyotype was also present in 40 metaphases of cultured fibroblasts. The Xp21 region appeared intact, with no evidence of duplication. Skeletal survey and MRI of the brain were normal. Vaginogram and voiding cystourethrogram demonstrated a uterus and normal urethra. At 15 months, the patient had a laparotomy to remove the gonads. Normal Fallopian tubes and uterus were present. Histologic examination of the gonads documented "streak" gonads consisting of ovarian stroma without evidence of oocytes.

She was re-examined at 9 years (Fig. 1). Her weight was 17 kg (<5th centile; 50th centile for 5 years); height 109 cm (<5th centile; 50th centile for 4 years). Multiple pterygia of the neck, axilla, elbows, knees, and interdigital spaces of the fingers and toes were present. There was mild left facial asymmetry with a broad forehead, ptosis of the eyelids, deviation of the nose to the left, and micrognathia. The ears were apparently low-set and posteriorly angulated. There was mild clitoromegaly and the labia were hypoplastic. Skin dimples were present in the presacral area and on the lateral aspects of both buttocks. An exaggerated lumbar lordosis was noted. She had unintelligible speech; however, she was able to communicate to some degree by signing. Intellectual abilities were in the moderate range of mental retardation.

Molecular studies using PCR with DNA primers flanking multiple regions of the Y chromosome confirmed that there was no deletion. Portions of the SRY gene located in the conserved DNA-binding domain high mobility group (HMG)-box were sequenced and no mutation was detected.

Fluorescence in situ hybridization (FISH) studies were performed using microsection slides of paraffin-embedded left and right ovaries obtained from prior surgery. A control testis and a control ovary were also studied. Cells were hybridized with X and Y chromosome probes (VYSIS Tri-Color CEP mixture 18 SA/X SG/Y SO, #32-111065, Lot/Ch.-B: 4309). FISH analysis of the patient's left and right ovaries revealed the presence of one green signal for one X chromosome and one orange signal for one Y chromosome in each cell.

DISCUSSION

Normal human sex differentiation consists of three basic steps [Jost, 1953, 1960, 1972]. Each of these steps involves a number of complex, sequential processes. The first step is the establishment of genetic sex, which is determined at fertilization. In the second step an indifferent gonad differentiates into a testis in the XY male or an ovary in the XX female. In the absence of the

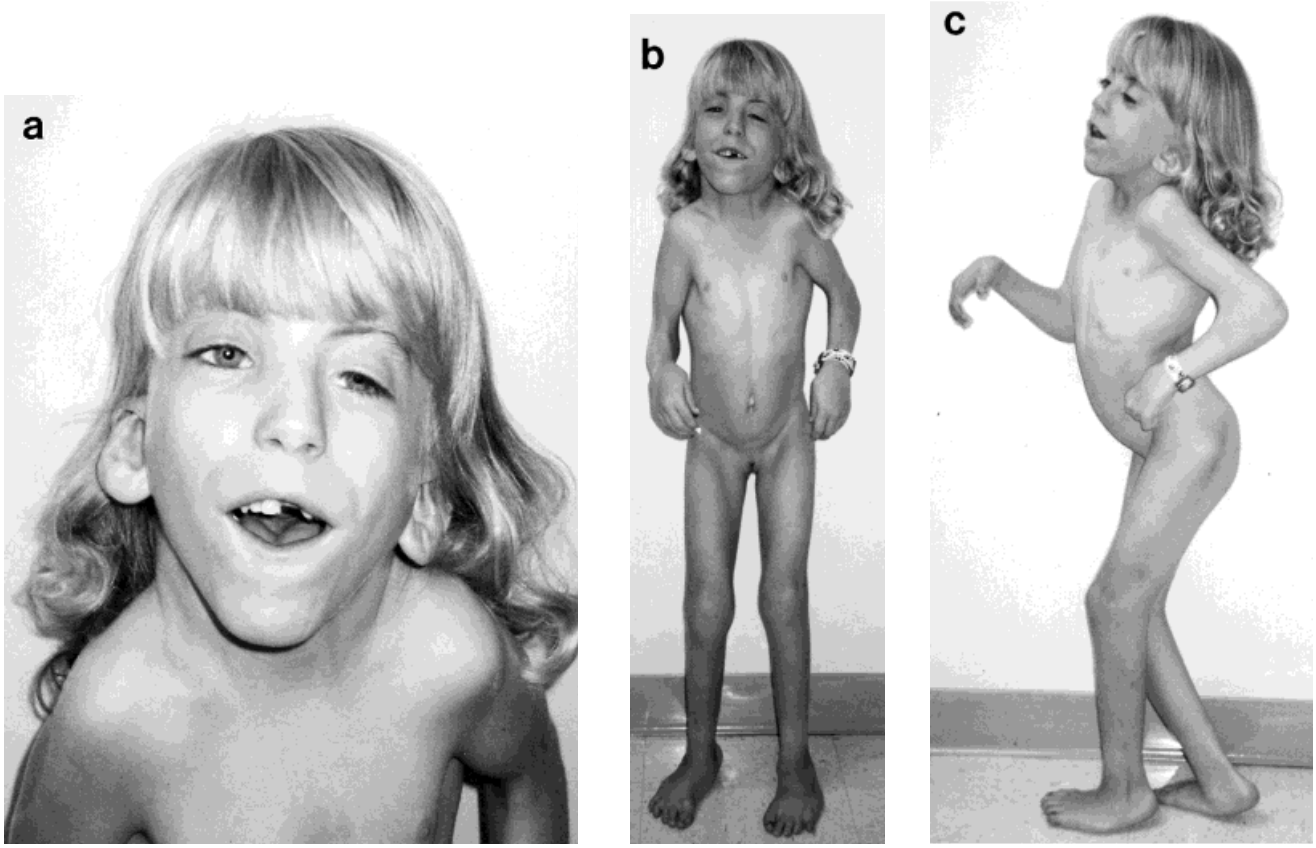

Fig. 1. **a,b,c**: Nine-year-old girl with XY gonadal dysgenesis and webbing of the neck, elbows, and knees, joint contractures, camptodactyly, ptosis, and downslanted palpebral fissures, mild facial asymmetry, and posteriorly angulated, apparently low-set ears.

Y chromosome, a testis-determining pathway fails to be initiated or is blocked, and development of the fetal gonads follows an inherent ovarian pathway. Testis development from the embryonic bipotential gonad depends on the inheritance of a Y chromosome-encoded gene, which was previously referred to as the testis-determining factor (TDF) and subsequently identified as the SRY (sex-determining region Y) gene [Sinclair et al., 1990]. SRY most likely activates a succession of other genes that switch the inherently female pattern of development to that of the male, beginning with testis formation. The final step in the pathway of normal sexual differentiation, the translation of gonadal sex into phenotypic sex, depends on the type of gonad formed. Indifferent internal and external genital precursors are converted to male or female structures, depending on whether or not a testis develops (with notable exceptions exemplified by the testicular feminization syndrome). Hormones produced by the fetal testis are responsible for the induction of masculinization of the external genitalia and development of the structures of the male reproductive tract, as well as prevention of the development of the uterus and fallopian tubes.

XY gonadal dysgenesis (also referred to as "pure XY" gonadal dysgenesis) is a disorder in which phenotypic females have a 46,XY chromosomal complement. Failure of testicular differentiation occurs in genetic males, resulting in nonvirilized female external genitalia and persistent Müllerian derivatives, including uterus, cervix, and Fallopian tubes. The oocytes of these patients degenerate, resulting in atresia of the follicles. The gonadal remnants persist as "streaks" of connective tissue. These "streak" gonads have a high risk of neoplastic transformation.

Swyer [1955] was the first author to document cases of XY gonadal dysgenesis, and this condition was initially referred to as Swyer syndrome. Over 120 cases of XY gonadal dysgenesis have been reported [Bercu and Schulman, 1980]. Sporadic cases occur, but many have been familial, compatible with autosomal recessive inheritance limited to karyotypic males or X-linked recessive inheritance [Simpson et al., 1971; German et al., 1978; Nazareth et al., 1979; Hersh et al., 1980; Phansey et al., 1980; Simpson et al., 1981].

The pathogenesis of the XY gonadal dysgenesis phenotype appears to be heterogeneous, resulting from a variety of defects in the testis-determining/differentiation pathway. Some XY females with gonadal dysgenesis have lost the sex-determining region of the Y chromosome by terminal exchange between the sex chromosomes [Levilliers et al., 1989] or by other deletions [Page et al., 1990]. Approximately 10–15% of sex-reversed XY females without a Y chromosome deletion have mutations in the SRY gene [Berta et al., 1990; Jager et al., 1990; Hawkins, 1993; Guidozzi et al., 1994; Schmitt-Ney et al., 1995]. With one exception [Tajima et al., 1994], SRY mutations cluster in the DNA segment encoding the high mobility group domain of the SRY protein [Schmitt-Ney et al., 1995]. In other cases, the phenotype may result from mutations in the regulatory regions of the SRY gene [Schmitt-Ney et al., 1995], or X-chromosomal or autosomal mutations in genes involved in sex determination downstream of SRY in the testis-determining pathway.

X-linked genes have been implicated in several familial cases of XY gonadal dysgenesis. Duplication of the Xp21 region causes sex reversal and multiple congenital abnormalities including mental retardation [Arn et al., 1994; Bardoni et al., 1994]. The severity of the abnormalities appears to depend upon the extent of the duplication. An autosomal sex reversal locus, SRA1, has been identified in XY females with campomelic syndrome [Tommerup et al., 1993]. Another autosomal sex reversing gene is located on 9p [Bennett et al., 1993]. A gene that regulates SRY has not yet been discovered. Regulation of SRY may involve the autosomal or X-linked genes described, or an unknown locus. Thus, XY gonadal dysgenesis is a heterogeneous phenotype.

Whereas most individuals with XY gonadal dysgenesis have a normal female phenotype and do not have other anomalies, some patients with extragenital abnormalities have been reported. Simpson et al. [1981] reported XY gonadal dysgenesis associated with campomelic dysplasia and with renal disorders. Simpson et al. [1982] later described a patient with XY gonadal dysgenesis, myotonic dystrophy, and end-stage renal disease. Moorthy et al. [1987] reviewed six previously reported patients with XY gonadal dysgenesis and renal failure and suggested the term "Frasier syndrome" after Frasier et al. [1964], who described two affected patients in 1964.

Gardner et al. [1970] reported on a 46,XY female with cleft palate, micrognathia, kyphoscoliosis, and clubfoot. Subsequently, Greenberg et al. [1987] reviewed these and 11 additional patients and suggested that they represented a recognizable syndrome that might be inherited in an autosomal recessive or X-linked recessive manner and designated it as the Gardner-Silengo-Wachtel or genito-palato-cardiac syndrome. Brosnan et al. [1980] described two 46,XY sisters with unusual face, cardiac, renal, musculoskeletal (acromelia with broad hands and feet, hypermuscular appearance), and ectodermal (scalp defects and unusual whorl patterns) anomalies. Silengo et al. [1974] described a 46,XY female infant with minor anomalies and limb abnormalities.

Our patient had a female phenotype with multiple pterygia. In their review, Hall et al. [1982] described 15 entities with limb pterygia, including autosomal dominant and recessive disorders.

The earliest complete description of one of these conditions, multiple pterygium syndrome, is generally credited to Matolscy [1936]. The designation multiple pterygium syndrome was used by Gorlin et al. [1976] to describe an autosomal recessive disorder that is characterized by pterygia of the neck, antecubital, and popliteal areas; syndactyly of the fingers; numerous congenital joint contractures; and talipes equinovarus. Other anomalies may include vertebral segmentation anomalies, scoliosis, and short stature. Multiple minor facial anomalies are present in most cases, including downward-slant of palpebral fissures, epicanthal folds, and ptosis. Intelligence is normal in these patients.

Chen et al. [1980] emphasized the heterogeneity of multiple pterygium phenotype. Although most cases appear to be due to autosomal recessive inheritance, autosomal dominant cases have been documented [Frías et al., 1973; McKeown and Harris, 1988]. With the exception of a case of 47,XXY/48,XXXY mosaicism with multiple joint webbing, aniridia, and mental retardation [Pashayan et al., 1973], no chromosome abnormalities have been reported in patients with multiple pterygium syndrome.

Multiple pterygia, facial anomalies, and joint contractures are common to all forms of multiple pterygium syndrome. In contrast to normal intellect in the autosomal recessive form, mental retardation has been described in some patients with the autosomal dominant form.

Our patient appears to be the first reported case of XY gonadal dysgenesis associated with multiple pterygia. It is possible that in this case, the nongenital abnormalities are coincidental. Therefore, the existence of two genetic disorders, including both XY gonadal dysgenesis and an autosomal dominant form of multiple pterygium syndrome in which mental retardation is a component in the same patient, cannot be excluded. However, since XY gonadal dysgenesis can be associated with other anomalies, or be part of recognizable conditions, heterogeneity of XY gonadal dysgenesis may exist. Therefore, in our patient, the presence of XY gonadal dysgenesis, multiple pterygia, short stature, microcephaly, and mental retardation may represent a new syndrome. Since no deletion in the Y chromosome or mutation in the SRY gene was detected in our patient, an unknown X-linked or autosomal gene involved in the sex-determination pathway may have been responsible for causing both XY gonadal dysgenesis and the phenotype of multiple pterygium, growth deficiency, microcephaly, and mental retardation. Identification of other patients with XY gonadal dysgenesis and similar nongenital anomalies would support the premise that these conditions may be related pathogenetically.

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